REMARKS

Introductory Comments:

Claims 1-5, 7-9, 29, 36, 38 and 39 were examined in the Office Action dated January 31, 2000. The Office rejected claims 1-5, 7-9, 36, 38 and 39 under 35 U.S.C. §103(a), as obvious. The Office objected to claim 29 as being dependent on a rejected claim but indicated that the claim would be allowable if rewritten in independent format. The rejections and objection are believed to be overcome by the above amendments and are otherwise traversed for the reasons discussed below.

Overview of the Above Amendments:

Claim 1 has been amended to recite the invention with greater particularity and specifically to define the size of the oil droplets in the composition as "about 100 nm to about 750 nm" in diameter. Support for the amendment can be found in the specification at e.g., page 16, lines 21-22.

Claim 29 has been amended to read in independent format and incorporate the recitations of claim 1 from which it previously depended.

As discussed in the interview, new claims 40-48 have been added. These claims all depend from claim 29 which has been indicated as allowable, and further define the components of the composition used in the methods. These claims correspond to pending claims 2-9 and 36, 38 and 39.

Thus, no new matter has been added to the application by way of the above amendments and new claims.

Formal Matters

The Office objected to the previously submitted Declaration because it included non-initialed and non-dated markings. The Office also requested an updated copy of a Power of Attorney. Applicants are submitting a Substitute Combined Declaration and Power of Attorney for Continuation-in-Part Application, signed by the inventors, as requested.

Rejections Under 35 U.S.C.§ 103(a)

Claims 1-5, 7-9, 36, 38 and 39 were rejected under 35 U.S.C. 103(a), as being unpatentable over Woodard et al., *Vaccine* 3:137-145 (1985) ("Woodard"), in view of Silvestri et al., *International Journal of Pharmaceutics*, 50:141-146 (1989) ("Silvestri") in the Office Action dated January 31, 2000, for reasons of record. In support of the rejection, the Office asserts that both Woodard and Silvestri suggest the desirability of making stable oil-in-water emulsions by varying various parameters, including droplet size. The Office concludes that "applicant has merely recognized a new use for an otherwise obvious composition." Office Action, page 4. Applicants respectfully traverse the rejection for reasons of record.

Moreover, as the Office has acknowledged, the references do not disclose adjuvant compositions consisting of the exact range amounts of metabolizable oil and emulsifying agent as claimed. (See, Paper No. 55, page 2.) Additionally, as evidenced by the accompanying Declaration of Dr. Ott, neither does the art suggest the particular compositions claimed. As explained in the interview, Woodard, the primary reference, actually teaches away from a composition as claimed. In particular, claim 1 (from which claims 2-5, 7-9, 36, 38 and 39 ultimately depend) pertains to adjuvant compositions consisting essentially of a metabolizable oil, wherein the oil is present in an amount of 0.5% to 20% of the total volume, and an emulsifying agent, wherein the emulsifying agent is 0.01% to 2.5% by weight (w/w), wherein the oil and the emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets substantially all of which are about 100 nm to about 750 nm in diameter. As explained in the interview and in the accompanying Declaration at paragraph 5, Woodard teaches that the amount of emulsifying agent necessary to obtain a stable emulsion, is 4% or greater; any amount less than 4% results in creaming, i.e., an unstable emulsion (see Table 2 on page 139, left column). Thus, Woodard's disclosure actually teaches away from the claimed compositions which include 0.01% to 2.5% (w/w) of emulsifying agent.

Furthermore, as explained in paragraph 5 of the accompanying Declaration, Woodard teaches that an antigen must be added to the internal phase (i.e., the oil phase in oil-in-water emulsions and the aqueous phase in water-in-oil emulsions), for optimal

antibody response; and that addition of the antigen to the external (continuous) phase reduces antibody production considerably (see Woodard, page 142, right column, 2nd paragraph). In order to "force" the antigen into the internal phase, the antigen is mixed with Woodard's oil and emulsifying agent prior to emulsification. Thus, Woodard's submicron oil-in-water emulsion does not exist without added antigen.

In contrast, and as discussed in the interview, while the claimed adjuvant composition is capable of increasing the immune response to an antigen when administered with the antigen, the antigenic substance is not present in the internal phase of the adjuvant composition. Thus, the claimed composition itself acts as an adjuvant, unlike Woodard's compositions which are merely delivery systems for antigens.

Additionally, the Office alleges that Silvestri teaches the desirability of submicron particles to improve the stability of oil-in-water emulsions. However, although Silvestri discloses that the stability of emulsions is improved by submicron size droplets, the reference does not suggest immunological adjuvant compositions in the form of an oil-in-water emulsion having droplets wherein substantially all of the droplets are about 100 nm to about 750 nm in diameter. The reference reiterates the teaching of Woodard, i.e., the submicron emulsions are used as drug delivery systems (see page 142, right column); but does not mention the use of submicron emulsions as adjuvants. Moreover, as discussed above, since Woodard suggests that emulsifying agent concentrations as claimed would render an unstable emulsion, the combination of Silvestri with Woodard, at best, would suggest an emulsion with emulsifying agent concentrations outside of the range of the claimed concentrations. Thus, the combination of Woodard with Silvestri does not provide any suggestion or motivation to one skilled in the art to prepare the claimed adjuvant compositions. Applicants therefore submit that the references, when considered in their entireties, do not render the claimed invention obvious. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

CONCLUSION

In view of the foregoing, applicants submit that the claims are now in condition for allowance and requests early notification to that effect.

Please direct all further communications regarding this application to:

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Currently Pending Claims

(08/418,870; 0085.006; 2302-0085.04)

1. (Eight times amended) An adjuvant composition consisting essentially of:

(1) a metabolizable oil, wherein the oil is present in an amount of 0.5% to 20% of the total volume and

(2) an emulsifying agent, wherein the emulsifying agent is 0.01% to 2.5% by weight (w/w), and wherein said oil and said emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets substantially all of which are about 100 nm to about 750 nm in diameter and wherein said composition exists in the absence of any polyoxypropylene-polyoxyethylene block copolymer and in the absence of any muramyl peptide, and further wherein said adjuvant composition is capable of increasing the immune response to an antigen when administered with the antigen.

2. The composition of Claim 1, wherein said oil is an animal oil.

3. The composition of Claim 2, wherein said oil is an unsaturated hydrocarbon.

4. The composition of Claim 1, wherein said oil is a terpenoid.

5. The composition of Claim 1, wherein said oil is a vegetable oil.

7. The composition of Claim 1, wherein said emulsifying agent comprises a non-ionic detergent.

8. (Amended) The composition of Claim 1, wherein said emulsifying agent comprises a polyoxyethylene sorbitan mono-, di-, or triester or a sorbitan mono-, di-, or triester.

9. (Amended) The composition of Claim 8, wherein said composition comprises .02 to

2.5 % by weight of said emulsifying agent.

29. (Four times amended) A method of stimulating an immune response in a host animal comprising:

administering an antigen to said animal in the presence of an immunostimulating amount of an adjuvant composition consisting essentially of:

(1) a metabolizable oil, wherein the oil is present in an amount of 0.5% to 20% of the total volume and

(2) an emulsifying agent, wherein the emulsifying agent is 0.01% to 2.5% by weight (w/w), and wherein said oil and said emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets substantially all of which are about 100 nm to about 750 nm in diameter and wherein said composition exists in the absence of any polyoxypropylene-polyoxyethylene block copolymer and in the absence of any muramyl peptide, and further wherein said adjuvant composition is capable of increasing the immune response to said antigen.

36. The composition of Claim 1 wherein said emulsifying agent comprises a polyoxyethylene sorbitan mono-, di-, or triester and a sorbitan mono-, di-, or triester.

38. The composition of claim 1 wherein the oil is present in an amount of 1% to 12% of the total volume and the emulsifying agent is 0.05% to 1% by weight (w/w).

39. The composition of claim 1 wherein the oil is present in an amount of 1% to 4% of the total volume and the emulsifying agent is 0.01% to 0.05% by weight (w/w).

40. (New) The method of Claim 29, wherein said oil is an animal oil.

41. (New) The method of Claim 40, wherein said oil is an unsaturated hydrocarbon.

42. (New) The method of Claim 29, wherein said oil is a terpenoid.

43. (New) The method of Claim 29, wherein said oil is a vegetable oil.

44. (New) The method of Claim 29, wherein said emulsifying agent comprises a non-ionic detergent.

45. (New) The method of Claim 29, wherein said emulsifying agent comprises a polyoxyethylene sorbitan mono-, di-, or triester or a sorbitan mono-, di-, or triester.

46. (New) The method of Claim 45, wherein said adjuvant composition comprises .02 to 2.5 % by weight of said emulsifying agent.

47. (New) The method of Claim 29 wherein the oil is present in an amount of 1% to 12% of the total volume and the emulsifying agent is 0.05% to 1% by weight (w/w).

48. (New) The method of Claim 29 wherein the oil is present in an amount of 1% to 4% of the total volume and the emulsifying agent is 0.01% to 0.05% by weight (w/w).